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Tranexamic acid reduces blood loss after primary shoulder arthroplasty: a double-blind, placebo-controlled, prospective, randomized controlled trial

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Background: Tranexamic acid (TXA) is an antifibrinolytic that has been shown to decrease blood loss and transfusion rates after hip and knee arthroplasty, with only limited evidence to support its use in shoulder arthroplasty. This study was conducted to determine whether intravenous (IV) TXA is more effective than placebo in reducing blood loss after primary total shoulder arthroplasty (TSA).

Methods: In this prospective, double-blind, placebo-controlled, randomized clinical trial, patients undergoing primary anatomic and reverse TSA were randomized to receive 1 g of intravenous TXA or a placebo of an equivalent volume of intravenous normal saline administered 10 minutes before the incision. The primary outcome measurement was calculated postoperative blood loss. Secondary outcomes included transfusion rates, weight of hemoglobin loss, hospital length of stay, and thromboembolic events.

Results: The study enrolled 110 patients, 2 of whom were excluded because they did not have a postoperative hemoglobin measurement, and the remaining 108 patients (52 for TXA, 56 for placebo) were analyzed. There were no significant differences between TXA and placebo groups in preoperative characteristics. For the primary outcome, the TXA group had significantly lower postoperative blood loss of 1100.9 ± 367.4 mL compared with 1274.5 ± 460.0 mL for the placebo group ($P = .03$). For secondary outcomes, TXA had lower weight of hemoglobin loss compared with placebo (152.2 ± 57.3 g vs. 178.0 ± 65.8 g; $P = .03$). No patients in the TXA or placebo groups required a transfusion.

Conclusions: Intravenous TXA reduced blood loss after primary TSA compared with placebo.

Anatomic and reverse total shoulder arthroplasty (TSA) is associated with the risk of moderate blood loss that can lead to transfusions. Average estimated intraoperative blood loss has been reported in the range of 354 mL to 361 mL, not accounting for additional blood loss postoperatively in soft tissues or surgical drains.[4,15] Transfusion rates of 2.4% to 9.5% have been reported for primary TSA.[4,11,15,16]

Tranexamic acid (TXA) is a synthetic antifibrinolytic agent that is an established method of reducing blood loss and transfusion requirement for patients undergoing total hip and knee arthroplasty.[2,3,7,13,22] TXA can be administered intravenously (IV), topically (intra-articularly), or orally, with most available literature addressing IV and topical administration. Systematic reviews and meta-analyses of the total hip and knee arthroplasty literature demonstrate an approximately 30% decrease in blood loss and a 50% decrease in the transfusion rate with topical or IV administration of TXA compared with placebo.[2,3,7,13,22] Moreover, the literature demonstrates no increased rate of thromboembolic or other complications associated with TXA administration for hip and knee arthroplasty.[7,22] Several recent studies have begun to explore the use of TXA in TSA patients to potentially reduce blood loss and transfusion.[1,6,8,14,19]

This study was conducted to determine whether IV TXA is more effective than placebo in reducing blood loss after primary TSA. We hypothesized that IV TXA would significantly reduce blood loss after TSA.

The Rush University Medical Center Institutional Review Board approved this study on April 10, 2015 (ORA Number: 14102308-IRB01).

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Materials and methods

Study design and patients

This prospective, double-blind, placebo-controlled, randomized clinical trial of IV TXA compared with placebo was registered at clinicaltrials.gov with registration number NCT02569658. The study was designed to determine the superiority of TXA over placebo by comparing 2 parallel groups: IV TXA and IV saline. A 1:1 allocation ratio of patients to TXA and placebo was used. There were no changes to the trial design during the study.

Patients were eligible for study inclusion if they were undergoing a unilateral primary anatomic or reverse TSA by the study authors at a single institution. Exclusion criteria were allergy to TXA, acquired disturbances of color vision, preoperative use of anticoagulant therapy within 5 days of surgery, history of arterial or venous thromboembolic disease (including deep venous thrombosis, pulmonary embolism, stroke, transient ischemic attack), ongoing pregnancy or breast-feeding, recent myocardial infarction (within 6 months before surgery), cardiac stent placement, renal impairment, hemophilia, refusal of blood products, revision TSA, TSA performed for the indications of acute proximal humeral fracture, or prior open shoulder surgery, including failed open reduction and internal fixation of proximal humeral fractures. Patients who underwent prior arthroscopic shoulder procedures were eligible to participate.

Patients who met eligibility criteria and consented to participate in the study by an informed consent process were randomized to receive 10 mL of IV normal saline placebo or 1 g of IV TXA diluted in 10 mL normal saline (X-Gen Pharmaceuticals, Inc., Horseheads, NY, USA). This dose of TXA was chosen because it is standard practice at our institution to administer 1 g IV TXA 10 minutes before the incision for total hip and knee arthroplasty.

A random number algorithm was used for the randomization process. The TXA or placebo was placed into an unlabeled 10-mL syringe by research pharmacy staff who were not involved in the patient's care to ensure identical appearance and blinding between TXA and placebo. A blinded research assistant delivered the syringe to the blinded anesthesiology staff, who administered the syringe was administered 10 minutes before the incision. All patients, surgeons, anesthesiologists, and clinical staff were blinded to the patient's study group allocation. Study group allocation remained blinded by the research pharmacists until the time of data analysis.

Data acquisition was performed by a research assistant blinded to patient study group allocation. Patient demographics and preoperative characteristics were recorded and compared between the TXA and placebo groups. Included were age, sex, American Society of Anesthesiologists (ASA) Physical Status Classification, body mass index, and preoperative hemoglobin.

Surgical technique and postoperative care

Anatomic or reverse TSA was performed by 5 fellowship-trained attending surgeons. Anesthesia involved interscalene regional anesthesia combined with general anesthesia. A deltopectoral approach was used, followed by implantation of uncemented anatomic or reverse TSA implants, according to attending surgeon preference. Drains were used postoperatively based on surgeon preference and removed on postoperative day 1 in all patients.

Patients underwent standard postoperative care, including admission to the hospital for at least 1 night. Patients were monitored by a hospitalist while in the hospital and received occupational therapy. Patients had sequential compression devices for deep venous thrombosis prophylaxis during their hospital stay. The patients underwent daily complete blood count, including measurement of hemoglobin, for as long as they remained in the hospital. Patients underwent transfusion if their postoperative hemoglobin dropped below 7.0 g/dL or for higher hemoglobin values only for specific medical indications specified by the consulting hospitalist attending.

Outcomes

The primary outcome for this study was postoperative blood loss based on a formula accounting for initial patient hemoglobin, the lowest postoperative hemoglobin, and patient blood volume approximated based on patient sex, height, and weight.[5,20] This method of calculating blood loss is intended to account for intraoperative and postoperative losses, including bleeding into soft tissues. It is felt to be more accurate than methods such as estimated blood loss and surgical drain losses.[5,20] The blood loss calculation formulas are as follows:

$$\mathrm{Hb(loss)} = \mathrm{BV} \times [\mathrm{Hb(i)} - \mathrm{Hb(e)}] \times 0.001 + \mathrm{Hb(t)}$$

$$\text{Blood loss} = 1000 \times \mathrm{Hb(loss)}/\mathrm{Hb(i)}$$

Where *Hb(loss)* is loss of hemoglobin in grams, *Hb(i)* is preoperative hemoglobin, *Hb(e)* is the lowest postoperative hemoglobin, and *Hb(t)* is total amount of transfused hemoglobin. *BV* is predicted blood volume, which is calculated as follows:

$$\mathrm{BV(male)} = (0.3669 \times \mathrm{Ht}^3) + (0.03219 \times \mathrm{Wt}) + 0.6041$$

$$\mathrm{BV(female)} = (0.3561 \times \mathrm{Ht}^3) + (0.03308 \times \mathrm{Wt}) + 0.1833$$

Where *Ht* is height in meters and *Wt* is weight in kilograms.

Secondary outcomes included transfusion rates, weight of hemoglobin loss, intraoperative estimated blood loss, and hospital length of stay. Postoperative complications, including thromboembolic events, were noted for a 90-day postoperative period. Complications were noted on routine postoperative follow-up examinations. A research assistant who was not involved in patient care and was blinded to patient study group allocation recorded data after patients were discharged from the hospital.

Statistical analysis

Power analysis was performed before study initiation to determine sample size. Using estimated intraoperative blood loss averaging 361 ± 220 mL for TSA from a recent report[4] and an estimated 30% reduction of blood loss based on total hip and knee arthroplasty literature,[2,3,7,13,22] we determined that a sample size of 110 patients (55 patients per group) was necessary to achieve power of 80% at an α of 5%.

Descriptive statistics are presented with mean ± standard deviation for continuous data and as frequency with percentages for categoric data. Data were tested for normality by Kolmogorov-Smirnov testing and found to be normally distributed, and therefore, parametric tests were used. Two-sample unpaired Student *t* tests were used to compare continuous variables, including calculated blood loss. The χ^2 and Fisher exact tests were used as appropriate based on expected values to compare categoric data. Significance was set at $P < .05$. Analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA).

Results

Patient enrollment and baseline data

During the enrollment period from September 2015 to November 2016, 376 patients underwent primary anatomic or reverse TSA. A Consolidated Standards of Reporting Trials flow diagram is shown in Fig. 1. Of these, 92 patients were ineligible based on exclusion